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PRE-APPEAL BRIEF REQUEST FOR REVIEW	Docket Number (Optional) REVEL15	
I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to "Mail Stop AF, Commissioner for Patents, P.O. Box 14550, Alexandria, VA 22313-1450" [37 CFR 1.8(a)] on _____ Signature _____ Typed or printed name _____	Application Number 09/462,416	Filed April 13, 2000
	First Named Inventor Michel REVEL	
	Art Unit 1649	Examiner D. Kolker

Applicant requests review of the final rejection in the above-identified application. No amendments are being filed with this request.

This request is being filed with a notice of appeal.

The review is requested for the reason(s) stated on the attached sheet(s).
Note: No more than five (5) pages may be provided.

I am the

- ☐ applicant/inventor
- ☐ assignee of record of the entire interest. See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96)
- ☒ attorney of record. Registration number 25,618.
- ☐ attorney or agent acting under 37 CFR 1.34. Registration number if acting under 37 CFR 1.34 _____

Signature

Roger L. Browdy
Typed or Printed Name

202-628-5197
Telephone number

April 14, 2006
Date

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

☐ *Total of _____ forms are submitted.

REASONS WHY REVIEW IS REQUESTED

Following the Advisory Action of March 17, 2006, in this case, the sole rejection remaining in the case is the rejection of claims 6, 9-11, 33 and 38 under 35 U.S.C. §103(a) as being unpatentable over Fischer et al (1995), Nature Biotechnology 15:142-145, in view of Weich et al (1994), Experimental Hematology 21:647-655.

The representative independent claim in this appeal is claim 38, which reads as follows:

> 38. A chimeric glycosylated soluble interleukin-6 receptor (sIL-6R)-interleukin-6 (IL-6) polypeptide (sIL-6R/IL-6), consisting of:
>
> an amino acid sequence which is a fusion product of sIL-6RδVal fused to IL-6, including a non-immunogenic linker of 3-4 amino acids therebetween or including a peptide of 13 amino acid residues of sequence Glu-Phe-Gly-Ala-Gly-Leu-Val-Leu-Gly-Gly-Gln-Phe-Met (SEQ ID NO: 1) therebetween, which linker does not prevent the chimeric polypeptide from triggering dimerization of gp130 in human cells.

It can be seen that this claim is directed to a polypeptide consisting of an amino acid sequence that is a fusion product of sIL-6RδVal fused to IL-6 with a linker therebetween, which linker does not prevent the chimeric polypeptide from triggering dimerization of gp130 in human cells. The linker is either (a) a non-immunogenic linker of 3-4 amino acids, or (b) a peptide of 13 amino acid residues of the sequence of SEQ ID NO:1.

Claims 4 and 7 have been indicated to be allowable if rewritten in independent form. Claim 7 is specifically directed to the polypeptide in which the linker is that of (b) above, i.e., the amino acid peptide linker of SEQ ID NO:1. Claim 4 is directed to a polypeptide in which the linker is the tripeptide sequence Glu-Phe-Met. Thus, the only polypeptides that have not been allowed are those in which the linker is a non-immunogenic linker of 3-4 amino acids other than Glu-Phe-Met. The examiner considers such polypeptides to be *prima facie* obvious from Fischer in view of Weich.

Fischer is directed to a polypeptide that is a fusion protein of soluble IL-6R and IL-6 linked by a flexible peptide chain. The differences between Fischer and the present

claims are that the N-Terminal Ig domain, as well as the C-terminal tether domain of the human sIL-6R were excluded as they had previously been shown not to contribute to ligand binding in biological activity of the IL-6R protein, and it was desirable to keep the overall size of the fusion protein as small as possible. The second difference is that the flexible linker is different. Fischer teaches in the paragraph bridging pages 142 and 143:

> We hypothesize that the formation of the IL-6/IL-6R complex could be greatly enhanced by converting it into a unimolecular protein using a flexible polypeptide as a linker (Fig. 1A). Using a 3-dimensional model of the complex, the distance between the C-terminus of IL-6R and the N-terminus of IL-6 was estimated to be in the order of 40Å [footnote omitted]. A similar distance between the parallel helices A and B in human growth hormone and human IL-6 is spanned by a flexible loop of about 33-36 residues [footnotes omitted]. We used the 16 N-terminal non-helical and presumably flexible amino acid residues of IL-6 together with a 13 residue sequence rich in glycine and serine [footnotes omitted] to connect IL-6 and the sIL-6R (Fig. 1B).

Thus, the flexible linker was a specific one of the sequence RGGGGSGGGGSVE.

The examiner cites Weich as teaching that 2-3 amino acid linkers generally are suitable for use in chimeric proteins comprising interleukin molecules. Weich teaches a fusion protein between interleukin-3 (IL-3) and erythropoietin (EPO). The abstract states that EPO acts synergistically with IL-3 to induce proliferation and differentiation of erythroid progenitors, and the fusion proteins were generated to determine whether optimal expansion of erythroid cells results when they are targeted by a molecule with both IL-3 and EPO activities. The fusion proteins of Weich were prepared using either short (2-3 aa) linkers, more specifically either Leu-Asp or Ala-Ala-Ala, or a long (23 aa) linker, specifically a linker that contains $(GGGGS)_3$ as its major component. See the paragraph bridging pages 649 and 650 of Weich. Weich discloses in the first full paragraph on the left column of page 653 that, whether using a short (2-3 aa) or long (23 aa) linker sequence, some functional activity is always maintained. However, in the first full paragraph on the right column of page 653, Weich teaches that, insofar as IL-3 binding by the fusion proteins is concerned, when IL-3 was linked to EPO by 2 or 3 aa, binding affinities were reduced compared to rhIL-3 alone, while the binding affinity of IL-3 linked to EPO by a 23 aa sequence rich in glycine and

proline equaled that of rhIL-3. This part teaches away from the use of short linkers. In any event, it is clear that Weich does not make any distinction based on the nature of the 2-3 aa short linker. The fusion proteins acted the same whether the short linker was Leu-Asp or Ala-Ala-Ala. The difference in results is in the size of the linkers, not the specific amino acids used in the short linker.

In the Advisory Action of March 17, 2006, the examiner stated:

> While the specific choice of EFM as a tripeptide linker is not taught or suggested by the cited references, Weich teaches that 2-3 amino-acid linkers generally are suitable for use in chimeric proteins comprising interleukin molecules. As set forth on p. 5 of the office action mailed 10/14/05, the overlap of ranges between the prior art (2-3 amino acids) and the claimed linker length (3-4 amino acids, see claim 38) provides basis for the selection of a linker of this size generically. Furthermore, the reference teaches that the size of the linker is not important, as linkers 2-3 amino acids or 23 amino acids long are both functional. Fischer discloses the distance between the two protein moieties to be "in the order of 40 angstroms" but nothing in Fischer teaches that linkers smaller than 13 amino acids (used by Fischer and by applicant) suggests that smaller linkers could not be used. In fact Fischer teaches that it is important to keep the overall size of the molecule small, so the finding that a 3-mer linker worked is not at all surprising given the teachings of both Fischer and Weich.

It is believed that there is a clear error in the examiner's rejection as the examiner's suggested motivation for combining the references cannot stand up to scrutiny.

Those of ordinary skill in the art would have no motivation to combine Weich with Fischer as both references teach away from the combination that the examiner considers to be obvious and because there would be no motivation to combine a teaching that relates to fusion proteins of two completely different proteins (IL-3/EPO versus sIL-6R/IL-6).

Fischer explicitly discloses that they select their 13 residue flexible linker specifically in light of their finding that using a 3-dimensional model of the complex, the distance between the C-terminus of IL-6R and the N-terminus of IL-6 was estimated to be in the order of 40Å. This is a teaching that it is important in order to maintain the activity intended for the ligand-receptor fusion protein that this distance be maintained. The examiner states in the Advisory Action that there is nothing in Fischer that teaches that

linkers smaller than 13 amino acids could not be used. However, to the contrary, Fischer teaches that this length was specifically chosen in order to maintain this distance, and there is no suggestion to one of ordinary skill in the art that choosing a length that will not maintain this distance would be expected to work. Despite Fischer's disclosure that it is useful to keep the overall size of the fusion protein as small as possible, Fischer does not attempt to use a small linker, such as only 3 amino acids. No one of ordinary skill in the art reading Fischer would consider the use of a smaller linker to be obvious and would consider that Fischer teaches away from using such a small linker because of the disclosure of the necessity to maintain a distance between the C-terminus of IL-6R and the N-terminus of IL-6 on the order of 40Å.

The first paragraph of Fischer teaches that there are certain cells that are responsive toward the combination of IL-6 and sIL-6R but not to IL-6 alone, and that these include hematopoietic progenitor cells and neuronal cells. The purpose of the fusion product of IL-6 and sIL-6R in Fischer is, therefore, to stimulate human hematopoietic progenitor cell expansion, i.e., bind to the appropriate receptor on the hematopoietic progenitor cells. In contrast, Weich discloses a completely different fusion protein that does not involve an interleukin and its receptor, but involves two separate and distinct cytokines, i.e., IL-3 and EPO. It has been found that EPO and IL-3 each induce proliferation and differentiation of erythroid progenitors, but the use of both together acts synergistically. Thus, the fusion protein was attempted. However, there would have been no suggestion to anyone of ordinary skill in the art reading Weich and Fischer that the physical constraints involved in binding and maintaining biological activity of EPO and IL-3 might be the same as those involved in constraining the receptor-ligand complex sIL-6R/IL-6. As indicated above, Fischer specifically teaches physical reasons why a long linker is desirable. The considerations of Weich are irrelevant as those of ordinary skill in the art reading the two would have no reason to believe that a linker that works with IL-3/EPO would be expected to work with the completely different combination of sIL-6R/IL-6.

Furthermore, as indicated above, Weich teaches that, insofar as binding of the fusion proteins is concerned, the longer linker works better than the shorter linker. Accordingly, the examiner has not established a *prima facie* case that establishes the appropriate motivation for one of ordinary skill in the art to use the less preferred linker of Weich when it relates to EPO and IL-3 as a substitute for the specifically preferred linker of Fischer, which deals with two completely different proteins, i.e., sIL-6R and IL-6.

Additionally, it is inconsistent for the examiner to allow the specific choice of EFM as a tripeptide and refuse to allow any other tripeptide. Fischer would tend to suggest that a short linker is a short linker, and there is no criticality in the specific amino acids thereof. Thus, all tripeptide linkers should be allowable for the same reason that the examiner has found the EFM tripeptide linker to be allowable (claim 4).

For all of these reasons, it is urged that this rejection be withdrawn following a pre-appeal brief conference.